

clinical settings. Alpern and Dowell,¹⁰⁹ for example, reported on patients with nonhistotoxic clostridial bacteremia whose underlying diseases included various pulmonary disorders, congestive heart failure, bleeding peptic ulcer, cirrhosis and iron deficiency anemia. The bacteremia was seemingly benign in some cases since ten of 12 patients who did not receive antibiotics survived. Gorbach and Thadepalli⁷⁶ also made this observation in their patients at Cook County Hospital. They were able to evaluate 29 patients with blood cultures positive for clostridia including some histotoxic strains. Whereas twelve of the 29 patients had soft tissue infections involving clostridia, a number of patients had underlying diseases not usually associated with clostridial infection. These include six patients with aspiration pneumonia, two with cavitary tuberculosis, two with a seizure disorder and one with meningococcemia. Why clostridial bacteremia should develop in these patients is an interesting but unanswered question.

Management of clostridial soft tissue infection is as varied as the infectious syndromes these agents may cause. Appropriate drainage of focal infection and administration of penicillin are the cornerstones of therapy. With more serious infection, aggressive therapeutic intervention is indicated.

Therapy of Clostridial Myonecrosis

ARTHUR A. SCHWARTZ, MD*

SUCCESSFUL THERAPY of patients with clostridial myonecrosis depends in great measure on the general state of health of the patient and the rapidity with which the diagnosis is made. Delay in the initiation of therapy may yield catastrophic results.⁶²

Appropriate surgical management of clostridial myonecrosis includes several therapeutic modalities. While the relative importance of each of the following aspects of treatment remains a topic of controversy, many authorities agree that combinations of (1) surgical debridement, (2) antibiotic therapy, (3) hyperbaric oxygen and (4) supportive measures are necessary. The ad-

ministration of polyvalent antitoxin has not been shown to be effective, and many centers have discontinued use of the antitoxin because of the risk of hypersensitivity phenomena.¹¹⁰

Surgical debridement is included by virtually all authors as a cornerstone of therapy. The time of operation and extent of debridement is less clear. Altemeier suggests wide, emergent debridement with multiple incisions and appropriate fasciotomies.⁶² Roding and co-workers recommended limiting emergent surgical therapy to opening the original wound and incising abscesses.¹¹¹ These authors suggest delaying definitive surgical procedures until demarcation of necrosis occurs, with the hope of limiting disfigurement.¹¹¹ Early surgical intervention not only may allow decompression but also, as noted above, facilitates early diagnosis.

The role of antibiotics is somewhat less clear. The drug of choice is aqueous penicillin in doses of 20 million units per day. While the efficacy of penicillin is difficult to delineate, animal models have suggested the beneficial effect of antibiotics.¹¹² Second line drugs, to be used in patients allergic to penicillin, include cephalosporins, chloramphenicol and erythromycin. Sensitivity testing is advisable, especially if tetracycline, another macrolide, clindamycin or carbenicillin is being used.¹¹¹

Hyperbaric oxygen has been shown to decrease mortality, and has been suggested to limit tissue necrosis. Positive results using hyperbaric oxygen have been obtained from several laboratories.¹¹¹⁻¹¹⁴ In an experimental study, Demello and co-workers showed the value of 100 percent oxygen at three atmospheres, but also showed that for maximum effectiveness in their model, debridement and antibiotics should be used.¹¹²

Supportive measures should include careful medical management as well as anticipation and prompt therapy of complications of clostridial bacteremia.

Management of these patients frequently involves volume expansion with intravenous fluid, plasma and blood. Shock is a frequent complication and rapid volume expansion may be necessary. Monitoring central venous pressure or (more reliably) pulmonary capillary wedge pressure may be of value in severely ill patients. The role of steroids remains somewhat controversial. Additionally, careful monitoring of the electrolytes and packed cell volume may avert potential com-

*Department of Surgery, Harbor General Hospital, Torrance, and Assistant Professor of Surgery, UCLA.

plications. Acute tubular necrosis is a not uncommon sequela of the shock and should be treated appropriately.

Hemolysis (especially in uterine myonecrosis) may be severe and require aggressive transfusion therapy.

Gas gangrene is a potentially preventable disease. Attention to good surgical principles is of primary importance with adequate debridement being the cornerstone of prevention. Antitoxin is ineffective as a prophylactic measure.

Summary

DAVID K. HENDERSON, MD: *The severity of all these syndromes depends in great measure on the potent toxins elaborated by these organisms. C botulism and C tetani produce neurotoxins while the histotoxic clostridia produce numerous toxins, most notably phospholipase C, which are responsible for the extensive tissue destruction seen in the severe soft tissue infections.*

Specific antitoxins have been developed to counteract the effect of these toxins. These antitoxins, however, have met with limited success in the therapy of the clostridial-induced emergencies. Type B botulism antitoxin has been shown to be effective and hyperimmune antitetanus globulin is of value both in wound prophylaxis as well as in the therapy of tetanus. The efficacy of other antitoxins remains to be shown. Specific effective pharmacologic therapy for these syndromes, with the possible exception of guanidine in botulism, has yet to be developed.

Success in the management of each of these syndromes depends to a great extent upon rapid, accurate clinical diagnosis and the prompt initiation of both specific and nonspecific therapeutic measures. In the neuromuscular syndromes, supportive care, particularly meticulous respiratory care, remains the cornerstone of therapy. Surgical debridement and drainage are of primary importance in the serious soft tissue infections.

Several areas of controversy remain to be clarified. The use of guanidine in botulism, the value of polyvalent antitoxin in myonecrosis and the use of antibiotics in all these syndromes are among those topics which need further study.

Each of these syndromes can be devastating and for that reason the clinician should maintain a high index of suspicion in the appropriate set-

ting. Prompt diagnosis and therapy may prevent the development of a life-threatening toxic emergency.

REFERENCES

1. Meyer, KF: The status of botulism as a world health problem. Bull World Health Org 15:281-298, Jan 1965
2. Meyer KF, Eddie B: Fifty Years of Botulism in the United States and Canada. San Francisco, George Williams Hooper Foundation, University of California, 1950
3. Reimann H: Botulism, In Reimann H (Ed): Food-Borne Infections and Intoxications. New York, Academic Press, 1969, pp 291-327
4. Dolman CE, Murakami L: *Clostridium botulinum* type F, with recent observations on other types. J Infect Dis 109:197-227, Aug 1961
5. Meyer KF: The rise and fall of botulism (Editorial). Calif Med 118:63-64, May 1973
6. Jensen LB: Botulism, In Jensen LB (Ed): Poisoning Misadventures. Springfield, IL, Charles C Thomas, 1970, pp 64-71
7. Duff JT, Wright GG, Yarinsky A: Activation of *Clostridium botulinum* type E toxin by trypsin. J Bacteriol 72:455-460, Oct 1967
8. Sakaguchi G: Botulism—Type E, In Reimann H (Ed): Food-Borne Infections and Intoxications. New York, Academic Press, 1969, pp 329-358
9. Koenig MG, Spickard A, Cardella M, et al: Clinical and laboratory observations of type E botulism in man. Medicine 43: 517-545, Sep 1964
10. Gangarosa EJ: Botulism, In Hoeprich PD (Ed): Infectious Diseases. Hagerstown, Md, Harper and Row, 1972, pp 1031-1036
11. Gutmann L, Pratt L: Pathophysiologic aspects of human botulism. Arch Neurol 33:175-179, Mar 1976
12. Lambert EH, Elmquist D: Quantal components of end plate potentials in the myasthenic syndrome. Ann NY Acad Sci 183:183-199, Sep 1971
13. Kao I, Drachman DB, Price DL: Botulinum toxin: Mechanism of presynaptic blockade. Science 193:1256-1258, Sep 1976
14. Center for Disease Control: Botulism in the United States, 1899-1973—Handbook for Epidemiologists, Clinicians, and Laboratory Workers, Jun 1974
15. Werner SB, Chin J: Botulism—Diagnosis, management and public health considerations. Calif Med 118:84-88, May 1973
16. Botulism, type F. Morbidity Mortality Weekly Report 15: 42, 359 Oct 1966
17. Moller V, Scheibel I: Preliminary report on the isolation of an apparently new type of *Clostridium botulinum*. Acta Pathol Microbiol Scand 48:80, Jan 1960
18. Koenig MG, Drutz DJ, Mushlin A, et al: Type B botulism in man. Am J Med 42:208-219, Feb 1967
19. Rogers DE: Botulism, vintage 1963. Ann Intern Med 61: 581-588, Sep 1964
20. Cherington M: Botulism: Ten year experience. Arch Neurol 30:432-437, Jun 1974
21. Dowell VR, Hawkins TM: Laboratory Methods in Anaerobic Bacteriology. US Dept of Health, Education and Welfare publication No. 73-8222, U.S. Government Printing Office, 1973
22. Merson MH, Hughes JM, Dowell VR, et al: Current trends in botulism in the United States. JAMA 229:1305-1308, Sep 1974
23. Merson MH, Gangarosa EJ, Dowell VR: More on botulism (Letter). Calif Med 119:65-66, Sep 1973
24. Merson MH, Dowell VR: Epidemiologic clinical and laboratory aspects of wound botulism. N Engl J Med 289:1005-1010, Nov 1973
25. Pickett J, Berg B, Chaplin E, et al: Syndrome of botulism in infancy: Clinical and electrophysiologic study. N Engl J Med 295:770-772, Sep 1976
26. California State Department of Public Health: Infant Botulism—a Newly Recognized Syndrome. 34, supplement, Sep 3, 1976
27. McQuillen MP, Cantor HE, O'Rourke JR, et al: Myasthenic syndrome associated with antibiotics. Arch Neurol 18:402-415, Apr 1968
28. Coleman GE, Meyer KF: Some observations on the pathogenicity of *B. botulinum*. J Infect Dis 31:622-649, 1922
29. Galpin JE, Chow AW, Bayer AS, et al: Sepsis associated with decubitus ulcers. Am J Med 61:346-350, Sep 1976
30. Cherington J, Rayon DW: Treatment of botulism with guanidine: Early neurophysiologic studies. N Engl J Med 282: 195-197, Jan 1970
31. Richer K, Doll W: Guanidinbehandlung des Botulismus. Z Neurol 198:332-341, Jun 1970
32. Faich GA, Graebner RW, Soto S: Failure of guanidine therapy in botulism A. N Engl J Med 285:773-776, Sep 1971
33. Robineau M, Modai J: Note preliminaire sur le traitement du botulisme par la guanidine: A propos d'un cas. La Presse Medicale 79:1169-1171, May 1971
34. Beck T, cited by Major RH (Ed): Classic Descriptions of Disease. Springfield, IL, Charles C Thomas, 1945, p 134
35. Adams EB, Laurence DR, Smith JWG: Tetanus. Oxford, Blackwell Scientific Publications, 1969, p 5
36. Weinstein L: Tetanus. N Engl J Med 289:1293-1296, Dec 1973

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37. Burrows W: Clostridium—The spore-forming anaerobes, In Textbook of Microbiology. Philadelphia, WB Saunders Co., 1973, p 617
38. Tarlov IM, Ling H, Yamada H: Neuronal pathology in experimental local tetanus. Neurology 23:580-591, Jun 1973
39. Adams EB, Lawrence DR, Smith JWG: Tetanus. Oxford, Blackwell Scientific Publications, 1969, pp 19-26
40. Keu JH, Corbett JL, Roberts-Pryor C, et al: Involvement of the sympathetic nervous system in tetanus. Lancet 2:236-241, Aug 1968
41. Kaeser HE, Saner A: Tetanus toxin: A neuromuscular blocking agent. Nature (Lond) 223:845, Aug 1969
42. Prophylaxis and treatment of tetanus and other clostridial wound infections. Med Lett Drugs Ther 15:39-40, Apr 1973
43. Blake PA, Feldman RA, Buchanan TM, et al: Serologic therapy of tetanus in the United States, 1965-1971. JAMA 235: 42-44, Jan 1976
44. Temper K: The use of diazepam in the treatment of tetanus. Am J Med Sci 266:5-12, Jul 1973
45. LaForce FM, Young LS, Bennett JV: Tetanus in the United States (1965-1966). N Engl J Med 280:569-574, Mar 1969
46. Reported Morbidity and Mortality in the United States, 1976. Atlanta, Center for Disease Control
47. Peebles TC, Levine L, Eldred MC, et al: Tetanus toxoid emergency boosters: A reappraisal. N Engl J Med 280:575-581, Mar 1969
48. Levinson A, Merske RL, Shein MK: Tetanus in heroin addicts. JAMA 157:658-660, Feb 1955
49. Mackae J: Tetanus. Br Med J 1:730-732, Mar 1973
50. Perlstein MA, Stein MD, Elam H: Routine treatment of tetanus. JAMA 173:1536-1541, 1960
51. Sykes MK, McNicol MW, Campbell EJM: Respiratory Failure, 2nd Ed. Oxford, Blackwell Scientific Publications, 1976
52. Safar P: Respiratory Therapy. Philadelphia, F. A. Davis Co., 1965
53. Bushnell SS: Respiratory Intensive Care Nursing. Boston, Little, Brown and Co., 1973
54. Cole L, Youngman H: Treatment of tetanus. Lancet 1: 1017-1019, May 17, 1969
55. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure in the adult. N Engl J Med 287:680-698, 743-752, 799-806, Oct 1972
56. Black LF, Hyatt RE: Maximal static respiratory pressures in generalized neuromuscular disease. Am Rev Resp Dis 103: 641-650, May 1971
57. Nyhan WL, Connor JD, Hamburger RN, et al: Tetanus (Specialty Conference). Calif Med 115:24-31, Oct 1971
58. Bennett JV: Tetanus—the role of diazepam in therapy (Editorial). Calif Med 115:51-52, Oct 1971
59. Selecky PA: Tracheostomy: A review of present-day indication, complications and care. Heart Lung 3: 272-280, Mar 1974
60. Kanarek DJ, Kaufman B, Zwi S: Severe sympathetic hyperactivity associated with tetanus. Arch Intern Med 132:602-604, Oct 1973
61. MacLennan JD: The histotoxic clostridial infections of man. Bacteriol Rev 26:177-276, Jun 1962
62. Altemeier WA, Fullen WD: Prevention and treatment of gas gangrene. JAMA 217:806-813, Aug 1971
63. Clarke JS, Bartlett JG, Finegold SM, et al: Bacteriology of the gut and its clinical implications. West J Med 121:390-403, Nov 1974
64. Lorber B, Swenson RM: The bacteriology of intra-abdominal infections. Surg Clin North Am 55:1349-1354, Dec 1975
65. Finegold SM, Bartlett JG, Chow AW, et al: Management of anaerobic infections. Ann Intern Med 83:375-389, Sep 1975
66. Chow AW, Marshall JR, Guze LB: Anaerobic infections of the female genital tract: Prospects and perspectives. Obstet Gynecol Survey 30:477-494, Jul 1975
67. Mentzer RM, Golden GT, Chandler JG, et al: A comparative appraisal of emphysematous cholecystitis. Am J Surg 129: 10-15, Jan 1975
68. Gorbach SL, Bartlett JG: Anaerobic infections. N Engl J Med 290:1177-1184, May 1974
69. Bartlett JG, Gorbach SL, Finegold S: The bacteriology of aspiration pneumonia. Am J Med 56:202-207, Feb 1974
70. Lorber B, Swenson RM: Bacteriology of aspiration pneumonia—A prospective study of community and hospital-acquired cases. Ann Intern Med 81:329-331, Sep 1974
71. Poppe JK: Intrapleural infection with *Clostridium welchii*. J Thorac Surg 13:340-344, Aug 1944
72. Lynch JP, Streider JW: Hemothorax complicated by infection with *Clostridium welchii*. N Engl J Med 226:685-687, Apr 1942
73. Bayer AS, Nelson SC, Galpin JE, et al: Necrotizing pneumonia and empyema due to *Clostridium perfringens*—Report of a case and review of the literature. Am J Med 59:851-856, Dec 1975
74. Isenberg HD, Lavine LS, Painter BG, et al: Primary osteomyelitis due to an anaerobic microorganism. Am J Clin Pathol 64:385-388, Sep 1975
75. Behr RC, Ward RM, Lien RH: Meningitis due to combined infections. Am J Dis Child 130:877-879, Aug 1976
76. Gorbach SL, Thadepalli H: Isolation of *Clostridium* in human infections: Evaluation of 114 cases. J Infect Dis 131 Suppl: S81-S85, May 1975
77. Brown RL, Peter G: Clostridial spontaneous peritonitis. JAMA 126:2095-2096, Nov 1976
78. Altemeier WA: Diagnosis, classification, and general management of gas-producing infections, particularly those produced by *Clostridium perfringens*, In Brown IW, Jr., Cox BG (Eds): Proceedings of the Third International Conference on Hyperbaric Medicine. Washington, DC, National Academy of Sciences, 1966, pp 481-491
79. Sim FH: Anaerobic infections. Ortho Clin North Am 6: 1049-1056, Oct 1975
80. Weinstein L, Barza MA: Gas gangrene. N Engl J Med 289:1129-1131, Nov 1973
81. Smith LP, McLean APH, Maughan GB: *Clostridium welchii* septicotoxemia. Am J Obstet Gynecol 110:135-149, May 1971
82. Bennett JM, Healey PJ: Spherocytic hemolytic anemia and acute cholecystitis caused by *Clostridium welchii*. N Engl J Med 268:1070-1072, May 1963
83. Moore A, Gottfried EL, Stone PH, et al: *Clostridium perfringens* septicemia with detection of phospholipase C activity in serum. Am J Med Sci 271:59-63 Jan 1976
84. Simpkins H, Kahlenberg A, Rosenberg A, et al: Structural and compositional changes in the red cell membrane during *Clostridium welchii* infection. Br J Haematol 21:173-812, Aug 1971
85. Caplan ES, Kluge RM: Gas gangrene—Review of 34 cases. Arch Intern Med 136:788-791, Jul 1976
86. Kerner M, Meakins JL, Wilson WE: Gas gangrene complicating limb trauma. J Trauma 16:106-110, Feb 1975
87. Brightmore T, Greenwood TW: The significance of tissue gas and clostridial organisms in the differential diagnosis of gangrene. Br J Clin Prac 28:43-50, Mar 1974
88. Duff HJ, McLean PH, McLean LD: Treatment of severe anaerobic infections. Arch Surg 101:314-317, Aug 1970
89. Baxter CR: Surgical management of soft tissue infections—Surg Clin North Am 52:1483-1499, Dec 1972
90. Adams RD, Denny-Brown D, Pearson CM: Diseases of Muscle. New York City, Harper & Row, 1961, pp 387-388
91. Isenberg AN: *Clostridium welchii* infection. Arch Surg 92: 727-731, May 1966
92. Lulu DJ, Rivera FJ: Gas gangrene. Am Surg 36:528-532, Sep 1970
93. Boggs DR, Frei E, Thomas LG: Clostridial gas gangrene and septicemia in four patients with leukemia. N Engl J Med 259:1255-1258, Dec 1958
94. Alpern RJ, Dowell VR: *Clostridium septicum* infections and malignancy. JAMA 209:385-388, Jul 1969
95. Poretz DM, Wood L, Park C: Adenocarcinoma of the colon presenting as *Clostridium septicum* infection of the left thigh. South Med J 67:862-864, Jul 1974
96. Jones LE, Wirth WA, Farrow CC: Clostridial gas gangrene and septicemia complicating leukemia. South Med J 53:863-866, Jul 1960
97. Wynne JW, Armstrong D: Clostridial septicemia. Cancer 29:215-221, Jan 1972
98. Propst A, Mose JR: Die Wirkung apathogener Clostridien auf bösartigen Tumoren. Z Krebsforsch 68:337-351, Nov 1966
99. Smucker EE, Redit SE, Harding HB: Spontaneous fatal gas gangrene septicemia. JAMA 174:898-900, Oct 1960
100. Clancy MT, O'Brien S: Fatal *Clostridium welchii* septicemia following acute cholecystitis. Br J Surg 62:518-519, Jul 1975
101. Soscia J, Grace WJ: Gas bacillus infections: Two unusual cases. Am J Dig Dis 10:625-630, Jul 1963
102. Himm HS, McLean AHP, Duff JH: Gas gangrene of the scrotum and perineum. Surg Gynecol Obstet 139:176-178, Aug 1974
103. McSwain B, Sawero JL, Lawler MR: Clostridial infections of the abdominal wall: Review of 110 cases. Ann Surg 163:859-863, Jun 1966
104. Ramsay AM: The significance of *Clostridium welchii* in the cervical swab and blood stream in postpartum and post-abortion sepsis. J Obstet Gynecol Brit Comm 56:247-258, Apr 1949
105. Butler HM: Bacteriological diagnosis of severe *Clostridium welchii* infection following abortion. Med J Aust 1:38-42, Jan 1941
106. Muller DA: *Clostridium welchii* infection in gynecology. So African Med J 38:539-541, Jul 1964
107. Pritchard JA, Whalley PJ: Abortion complicated by *Clostridium perfringens* infection. Am J Obstet Gynecol 111:484-492, Oct 1971
108. Eaton CJ, Peterson EP: Diagnosis and acute management of patients with advanced clostridial sepsis complicating abortion. Am J Obstet Gynecol 109:1162-1166, Apr 1971
109. Alpern RJ, Dowell VR: Non-histotoxic clostridial bacteremia. Am J Clin Pathol 55:717-722, 1971
110. Hook EW, Mandell GL: Other clostridial infections, In Thorn GW, Adams RD, et al (Eds): Principles of Internal Medicine, 8th Ed. New York, McGraw-Hill, 1977, pp 892-895
111. Roding R, Groenveld HA, Boerema I: Ten years of experience in the treatment of gas gangrene with hyperbaric oxygen. Surg Gynecol Obstet 134:579-585, Apr 1972
112. Demello FJ, Hagun JJ, Hitchcock CR: Comparative study of experimental *Clostridium perfringens* infection in dogs treated with antibiotics, surgery, and hyperbaric oxygen. Surgery 73: 936-941, Jun 1973
113. Sweiger JF, Shim SS: A comparison of the treatment of gas gangrene with and without hyperbaric oxygen. Surg Gynecol Obstet 136:969-970, 1973
114. Hart GB, O'Reilly RR, Cave RH, et al: The treatment of Clostridium myonecrosis with hyperbaric oxygen. J Trauma 14:712-715, Aug 1974